PB89-123038

Health and Environmental Effects Profile for N,N-Dimethylaniline

(U.S.) Environmental Protection Agency
Cincinnati, OH

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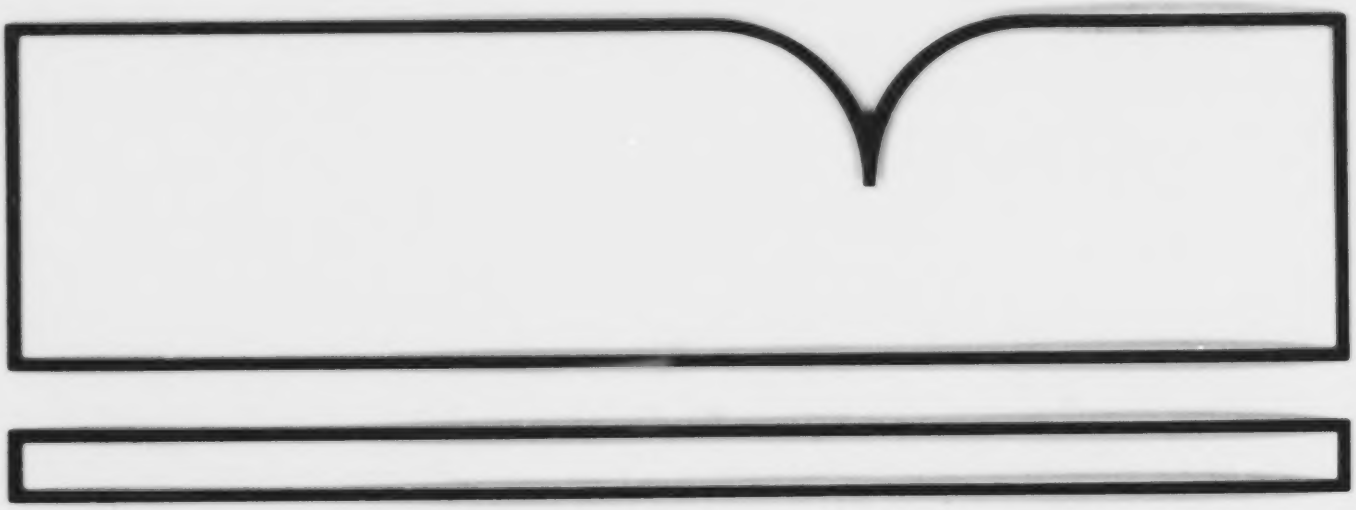

U.S. Department of Commerce
National Technical Information Service
NTIS

EPA/600/X-87/052
November, 1986

PB89-123038

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR N,N-DIMETHYLANILINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA
(Please read instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-87/052	2.
3. RECIPIENT'S ACCESSION NO	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for N,N-Dimethylaniline	5. REPORT DATE November 1986
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

The Health and Environmental Effects Profile for N,N-Dimethylaniline was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. N,N-Dimethylaniline has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for N,N-dimethylaniline is 0.002 mg/kg/day for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for N,N-dimethylaniline is 100.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 63
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

N,N-Dimethylaniline is a yellow liquid at ambient temperature that darkens in air (Northcott, 1978). It is soluble in ethanol or ether (Hawley, 1981) and is slightly soluble in water (Dragun and Helling, 1985; Amoore and Hautala, 1983). The solubility of this basic compound in water increases with decreasing pH of the water. The reported aqueous solubility values vary widely. Recent sources indicate that this chemical is currently produced by only two U.S. companies (SRI, 1985; USITC, 1985). Although the information on the recent U.S. production volume was not available, 13.6 million pounds of this chemical was produced in 1976 (Bannister et al., 1979). Commercially, N,N-dimethylaniline is produced by heating aniline with methanol in the presence of a catalyst at high pressure (Rosenwald, 1978; Northcott, 1978). It is used as an intermediate in the manufacture of vanillin, Michler's ketone and dyes, and is also used as an alkylating agent and a stabilizer (Hawley, 1981; Northcott, 1978).

The two processes that may be significant in determining the fate of N,N-dimethylaniline in water are photolysis and oxidation by singlet oxygen (Kondo, 1978; Young et al., 1973). The biodegradation of N,N-dimethylaniline in water may not be a significant process (Heukelekian and Rand, 1955; Malaney, 1960; Baird et al., 1977; Kitano, 1978). Based on its physical properties, it can be predicted that volatilization of this compound from water may be significant and that moderate amounts of the compound may be removed from the aquatic phase through sedimentation. The overall half-life (resulting from all processes) of N,N-dimethylaniline in river water was estimated to be 2.3 days (Zoeteman et al., 1980). This indicates that the

compound will be moderately persistent in river water. The bioconcentration potential for this chemical in aquatic organisms is low (Yoshida et al., 1983; Kawasaki, 1980; Sasaki, 1978).

Pertinent data regarding the fate and transport of N,N-dimethylaniline in the atmosphere could not be located in the available literature as cited in the Appendix. Based on its physico-chemical properties and its expected fate in water, it is predicted that photolysis and oxidation by HO radical will be the two important processes. Significant removal of atmospheric N,N-dimethylaniline through atmospheric physical processes is unlikely.

In soil, catalyzed oxidation of N,N-dimethylaniline may be a significant loss mechanism for this chemical (Dragun and Helling, 1985). Based on its physical properties it is speculated that this chemical may leach moderately into groundwater from contaminated soils.

Although N,N-dimethylaniline has been qualitatively identified in several industrial effluents and surface waters (U.S. EPA, 1976), it apparently has never been detected in drinking water. No monitoring data on the ambient level of N,N-dimethylaniline in either food or air were available. The level of this compound in the occupational atmosphere of a coal liquefaction plant and a plant manufacturing fiber glass-reinforced plastic pipe was reported (Harris et al., 1980; Markel and Wilcox, 1981); the compound was either not detected or its level was below the OSHA standard.

Quantitative data regarding the absorption of N,N-dimethylaniline could not be located in the available literature, although toxicity studies (Abdo et al., 1984; Markosyan, 1969) indicate that N,N-dimethylaniline is absorbed after both inhalation and ingestion. Pertinent data regarding the distribution, retention and excretion of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix. N,N-Dimethylaniline can

undergo oxidation at the nitrogen atom or either of the methyl carbons (Bickel et al., 1971). The rate of N-oxidation depends on the concentration of N-oxidase (Ohmiya and Mehendale, 1983). Conditions that increase the ratio of N-oxidation to C-oxidation may potentiate the tumorigenicity of carcinogenic aromatic amines (Odenbro and Arrhenius, 1984; Arrhenius, 1968). Metabolites of N,N-dimethylaniline found in the urine of dogs treated intravenously with 40 mg/kg of N,N-dimethylaniline included N,N-dimethylaniline, N-methylaniline, 4-aminophenol, 4-methylaminophenol, 4-dimethylaminophenol, 2-aminophenol, as well as minute amounts of 2-methylaminophenol and 2-dimethylaminophenol (Kiese and Renner, 1974). 2-Dimethylaminophenol has also been identified in the urine of rabbits (Hildebrandt, 1907) and rats (Elson et al., 1946). The appearance of the phenols indicate that N,N-dimethylaniline can also undergo oxidation at the ring carbons.

Pertinent data regarding the carcinogenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix, but a chronic gavage study in rats and mice is in progress (NTP, 1986). The mutagenicity of N,N-dimethylaniline has not been evaluated. No effects on survival or weight gain of dams, or birth weight, weight gain or viability of offspring were observed in mice treated by gavage with 365 mg/kg/day of N,N-dimethylaniline in corn oil on days 7-14 of gestation (Piccirillo et al., 1983). The chemical has not been studied adequately for teratogenicity. The final report on the subchronic phase of the NCI bioassay on N,N-dimethylaniline (Abdo et al., 1984; Springborn Institute for Bioresearch, Inc., 1980) indicated that splenomegaly and splenic hemosiderosis and hematopoiesis were observed in male and female rats treated by gavage (corn oil vehicle) with a dose of N,N-dimethylaniline $\geq$31.25 mg/kg/day (lowest dose tested) for 13 weeks. At dose levels $\geq$125 mg/kg/day, hepatic hemosiderosis was observed.

At higher dose levels, renal and testicular hemosiderosis was reported. Splenomegaly without splenic hemosiderosis was reported in half of the mice treated with 31.25 mg/kg/day (lowest dose tested) for 13 weeks. At the next highest dose tested (62.5 mg/kg/day), splenomegaly and splenic hemosiderosis occurred in 75% of the mice. Changes in the murine liver and kidney were reported only at the highest dose tested (500 mg/kg/day). The abstract of a Russian study (Markosyan, 1969) indicated that hematopoietic effects were observed in rats after continuous inhalation exposure to N,N-dimethylaniline for 100 days at 0.3 mg/m³ but not at 0.04 mg/m³.

The only toxicologically significant information concerning effects of N,N-dimethylaniline on aquatic organisms was provided by Tonogai et al. (1982), who reported 24- and 48-hour LC_{50} values of 56 and 33 mg/ℓ, respectively, for the medaka, Oryzias latipes, and by Broderius and Kahl (1985) who reported a 96-hour LC_{50} of 65.6 mg/ℓ for fathead minnows, Pimephales promelas.

An RfD (formerly called ADI) of 0.002 mg/kg/day or 0.2 mg/day for a 70 kg man was derived from the LOAEL of 31.25 mg/kg/day, 5 days/week in the subchronic gavage study by Springborn Institute for Bioresearch, Inc. (1980), using an uncertainty factor of 10,000. An RQ of 100 was based on the hematological effect of N,N-dimethylaniline in rats in the same subchronic oral study. Pending the results of a chronic oral bioassay in rats and mice (NTP, 1986), N,N-dimethylaniline was classified as a CAG Group D chemical because no data ragarding the carcinogenicity were available.

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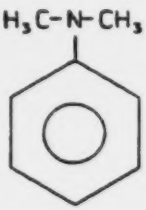
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BODT	Biological oxygen demand theoretical
CAS	Chemical Abstract Service
CS	Composite score
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LD_{Lo}	Lowest dose lethal to recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RFD	Reference Dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly called N,N-dimethylaniline is also known as N,N-dimethylbenzenamine, dimethylphenylamine, N-N-(dimethylamino)benzene and xylidene (SANSS, 1986). The structure, empirical formula, molecular weight and CAS Registry number for this compound are as follows:



Empirical formula: $C_8H_{11}N$

Molecular weight: 121.18

CAS Registry number: 121-69-7

1.2. PHYSICAL AND CHEMICAL PROPERTIES

N,N-Dimethylaniline is a yellow liquid at ambient temperature that darkens in air (Northcott, 1978). It is soluble in ethanol or ether (Hawley, 1981). Since N,N-dimethylaniline is a basic compound, its solubility is expected to be dependent on the pH of the aqueous medium. In water of pH >7, the solubility of this compound will be lower than in water of pH <5. The aqueous solubility data reported in the literature vary widely, possibly due to variations in the pH of the water; however, this cannot be ascertained because the pHs of the water used for measuring the solubilities were not reported. Following are some of the physical properties of this compound:

Melting point:	2°C	Verschueren, 1983
Boiling point:	192°C	Verschueren, 1983
Specific gravity:	0.96 at 20/4°C	Verschueren, 1983

Flash point (closed cup):	62.7°C	Hawley, 1981
Autoignition temperature:	370°C	Hawley, 1981
Vapor pressure, mm Hg:		
at 20°C	0.5	Chao et al., 1983
at 20°C	0.75	Weber et al., 1981
at 29.6°C	1.0	Chao et al., 1983
Water solubility, mg/ℓ:		
at 25°C	2000	Amoore and Hautala, 1983
at 25°C	1454.2	Huyskens et al., 1975
at 25°C	6606.9	Dragun and Helling, 1985
at 25°C	14,000.0	Dragun and Helling, 1985
unspecified temp.	1200	Yoshida et al., 1983
Log K_{ow}:	2.31	Hansch and Leo, 1985; Chiou et al., 1982; Freed and Haque, 1976
pK_a:	5.15 5.06	Huyskens et al., 1975 Nadolsky, 1978
Henry's Law Constant:	6.4×10^{-5} atm·m³ mol^{-1} (estimated)	Yoshida et al., 1983
Air odor threshold:	0.013 ppm	Amoore and Hautala, 1983
Water odor threshold:	0.025 ppm	Amoore and Hautala, 1983
Conversion factor:	1 ppm = 5.0 mg/m³	Verschueren, 1983

Chemically, N,N-dimethylaniline undergoes electrophilic substitution reactions. It can also react with HNO_2 to form ring-substituted nitroso compounds (Gutsche and Pasto, 1975). This compound is also susceptible to clay or soil-catalyzed free radical oxidation reactions (Dragun and Helling, 1985).

1.3. PRODUCTION DATA

According to the U.S. EPA (1977) TSCA Production File, eight U.S. chemical companies produced or imported N,N-dimethylaniline in 1977. As of January 1985, Buffalo Color Corp., Buffalo, NY, and DuPont Co. Inc., Deepwater, NJ, manufactured this chemical in the United States (SRI, 1985;

USITC, 1985). The recent information on the U.S. production volume for this chemical was not available, but 13.6 million pounds of N,N-dimethylaniline was produced in the United States in 1976 (Bannister et al., 1979).

N,N-Dimethylaniline is produced commercially by heating aniline at 300°C with methanol in the presence of a catalyst at high pressure. Sulfuric acid, phosphoric acid or alumina can be used as the catalyst (Rosenwald, 1978; Northcott, 1978).

1.4. USE DATA

N,N-Dimethylaniline is used as an intermediate in the manufacture of vanillin, Michler's ketone and dyes, and is also used as an alkylating agent and a stabilizer (Hawley, 1981; Northcott, 1978).

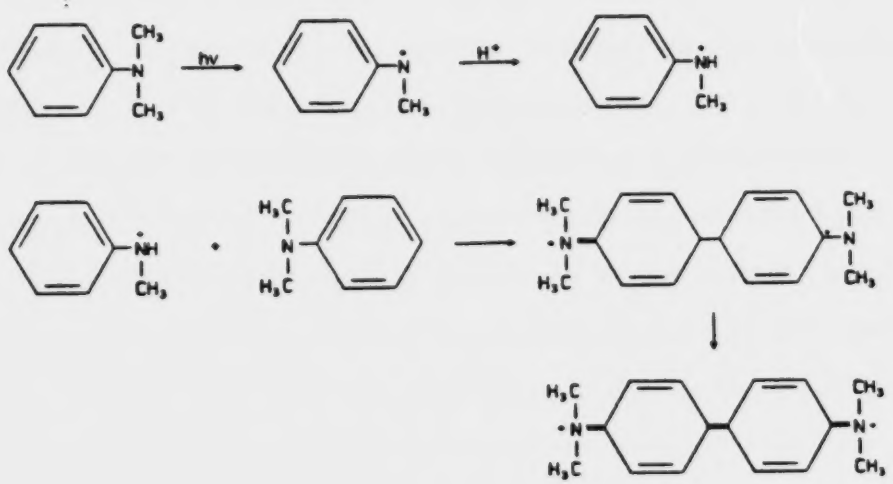
1.5. SUMMARY

N,N-Dimethylaniline is a yellow liquid at ambient temperature that darkens in air (Northcott, 1978). It is soluble in ethanol or ether (Hawley, 1981) and is slightly soluble in water (Dragun and Helling, 1985; Amoore and Hautala, 1983). The solubility of this basic compound in water is expected to increase with decreasing pH of the water. The reported aqueous solubility values vary widely. Recent sources indicate that this chemical is currently produced by only two U.S. companies (SRI, 1985; USITC, 1985). Although the recent U.S. production volume was not available, 13.6 million pounds of this chemical was produced in 1976 (Bannister et al., 1979). Commercially, N,N-dimethylaniline is produced by heating aniline with methanol in the presence of a catalyst at high pressure (Rosenwald, 1978; Northcott, 1978). It is used as an intermediate in the manufacture of vanillin, Michler's ketone and dyes, and is also used as an alkylating agent and a stabilizer (Hawley, 1981; Northcott, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

N,N-Dimethylaniline has its longest wavelength absorption band at 300 nm (Pac and Sakurai, 1968). Therefore, direct photolysis of this compound in sunlight is possible. The photolysis of N,N-dimethylaniline solution was studied by Pac and Sakurai (1968) with a high pressure mercury arc lamp. In the presence of acid, photolysis of N,N-dimethylaniline produced benzene, diphenyl, p-dimethylaminodiphenyl, bis(p-dimethylaminophenyl) methane and crystal violet. The pure sample, on the other hand, did not photolyze significantly. Photolysis of acidified N,N-dimethylaniline solution was also observed when UV light of wavelength >280 nm was used. Therefore, this study suggests the possibility of sunlight-induced photolysis of N,N-dimethylaniline in aqueous solutions of pH<7. The photolysis of air-saturated aqueous solutions of N,N-dimethylaniline in the acidic pH range was studied by McKellar (1967). With light flashes of unspecified wavelength, highly colored products were obtained that changed color depending on the pH of the solution; at pH 6-6.3, violet to brown products were obtained. The photolysis was postulated to proceed by the following mechanism:



The photodegradation of N,N-dimethylaniline in aqueous solution with fluorochemical lamps having continuous spectra from 300-400 nm (maximum intensity at 350 nm) was studied by Kondo (1978). The photodegradation half-life of the compound with this source of light was found to be <0.25 hour. Although no quantitative value can be assigned to the rate of disappearance of N,N-dimethylaniline when exposed to sunlight, the experiments of Kondo (1978) strongly suggest that photolysis may be a significant fate process for N,N-dimethylaniline in water.

The rate constants for the reaction of HO radical in aqueous solution with N,N-dimethylaniline were reported to be 5.3×10^9 M^{-1} sec^{-1} (Anbar et al., 1966; Anbar and Neta, 1967) and 8.9×10^9 M^{-1} sec^{-1} (Dorfman and Adams, 1973) at pH 9. If the concentration of HO radical in natural aquatic systems is assumed to be 10^{-17} M (Mill et al., 1982), the lower limit for the half-life of N,N-dimethylaniline will be ~90 days at pH 9. Therefore, in natural water having pH $\leq$9, this reaction may not be significant. The rate constant for the reaction/quenching of singlet oxygen ($^1\Delta_g$) with N,N-dimethylaniline was reported to be 7.3×10^7 M^{-1} sec^{-1} (Young et al., 1973). If the concentration of singlet O_2 in natural water is assumed to be 10^{-12} M (Mill et al., 1982), the half-life for this process is ~3 hours. Therefore, this reaction appears to be significant in controlling the fate of N,N-dimethylaniline in natural bodies of water.

The effect of chlorinating water containing N,N-dimethylaniline was studied by Jenkins et al. (1978). The chlorination produced <50% chlorinated products. No chloramine, ring fission or polymerization products were obtained; however, >50% of the total reaction product was not identified. The results of this experiment are important since drinking water is usually chlorinated for disinfection purposes.

The biodegradation of N,N-dimethylaniline was studied by several authors. Using sewage as microbial inoculum and the standard dilution method as the incubation method, degradation of only ~8% of the BODT was observed for N,N-dimethylaniline in 5 days (Heukelekian and Rand, 1955). Malaney (1960) used aniline-acclimated activated sludge as microbial inoculum and the Warburg method to study the rate of biodegradation of N,N-dimethylaniline. The oxygen uptake by the substrate at an initial concentration of 500 mg/ℓ amounted to ~16% of the BODT after 8 days of incubation. With activated sludge as microbial inoculum and Warburg respirometry as a measure of biodegradation, Baird et al. (1977) reported only 1% degradation of N,N-dimethylaniline (present at an initial concentration of 20 mg/ℓ) during a 6-hour period. All these results suggest that N,N-dimethylaniline is not readily biodegradable. The biodegradability of this compound was also tested by the Japanese test protocol (Kitano, 1978), which consists of incubating 100 ppm of test substance with activated sludge at 25°C for 2 weeks. N,N-Dimethylaniline was reported to be not degradable by this method.

Pertinent data regarding the loss of N,N-dimethylaniline from the aquatic phase by volatilization and sorption followed by sedimentation could not be located in the available literature as cited in the Appendix. Based on the Henry's Law constant for this compound of 6.4×10^{-5} atm·m^{3}mol^{-1} (see Section 1.2.) and the volatility characteristics associated with various ranges of Henry's Law constant (Lyman et al., 1982), it can be predicted that volatilization will not be rapid but may be significant. The K_{oc} for N,N-dimethylaniline has been estimated to be 817 (Yoshida et al., 1983). Therefore, sorption of this compound onto suspended particulate matters in water and removal through sedimentation may be moderate.

The overall half-life (resulting from all processes) of N,N-dimethylaniline in Rhine River water was estimated to be 2.3 days from the observed decrease in concentration of the chemical during a known length of the river (Zoeteman et al., 1980). This estimated half-life value indicates that N,N-dimethylaniline will be somewhat persistent in river water.

The BCF for N,N-dimethylaniline in aquatic organisms was estimated to be 14 (Yoshida et al., 1983). From the Japanese test procedure, the BCF for this compound was reported to be ~10 (Kawasaki, 1980). The low BCF value indicates that this compound will not bioconcentrate significantly in aquatic organisms. The low bioconcentration potential for N,N-dimethylaniline in aquatic organisms was also reported by Sasaki (1978).

2.2. AIR

Pertinent data regarding the fate and transport of N,N-dimethylaniline in the atmosphere could not be located in the available literature as cited in the Appendix. Based on its physico-chemical properties and its expected behavior in water, some predictions about its atmospheric fate and transport can be made. The two important processes that may significantly degrade this compound in the air are direct photolysis and oxidation by HO radical. The rate constant for N,N-dimethylaniline reaction with HO radical in the gas phase is reported to be 14.8×10^{-11} cm^3 $molecule^{-1}$ sec^{-1} at 25°C (Atkinson, 1985). If the concentration of HO radical in the atmosphere is assumed to be 10^6 molecules cm^{-3} (Cupitt, 1980), the half-life for this reaction can be estimated to be 1.3 hours; therefore, reaction of HO radical with N,N-dimethylaniline in the atmosphere is likely to be an important fate determining process. Based on its physical properties, it is speculated that significant removal of this compound, through atmospheric physical processes such as dissolution into raindrops or entrapment by snow, removal

through adsorption onto atmospheric aerosol particles and removal by sorption upon impaction at the earth's surface, will not be significant.

2.3. SOIL

The available information pertaining to the fate and transport of N,N-dimethylaniline in soil is limited. Based on its fate in water (see Section 2.1.), it is anticipated that biodegradation of this compound in soil may not be significant. Soil-catalyzed oxidation of N,N-dimethylaniline, however, may be a significant loss mechanism for this compound (Dragun and Helling, 1985), although the half-life of N,N-dimethylaniline resulting from this reaction cannot be estimated for the lack of quantitative reaction rate data. Based on the estimated loss of this compound from water (see Section 2.1.), it is likely that volatilization from soil may not be rapid. The moderate K_{oc} and water solubility of N,N-dimethylaniline indicate that this chemical may leach moderately into groundwater from contaminated soils.

2.4. SUMMARY

The two processes that may be significant in determining the fate of N,N-dimethylaniline in water are photolysis and oxidation by singlet oxygen (Kondo, 1978; Young et al., 1973). The biodegradation of N,N-dimethylaniline in water may not be a significant process (Heukelekian and Rand, 1955; Malaney, 1960; Baird et al., 1977; Kitano, 1978) Based on its physical properties, it can be predicted that volatilization of this compound from water may be significant and that moderate amounts of the compound may be removed from the aquatic phase through sedimentation. The overall half-life (resulting from all processes) of N,N-dimethylaniline in river water was estimated to be 2.3 days (Zoeteman et al., 1980). This indicates that the compound will be moderately persistent in river water. The bioconcentration potential for this chemical in aquatic organisms is low (Yoshida et al., 1983; Kawasaki, 1980; Sasaki, 1978).

Pertinent data regarding the fate and transport of N,N-dimethylaniline in the atmosphere could not be located in the available literature as cited in the Appendix. Based on its physico-chemical properties and its expected fate in water, it is predicted that photolysis and oxidation by HO radical will be the two important processes. Significant removal of atmospheric N,N-dimethylylaniline through atmospheric physical processes is unlikely.

In soil, catalyzed oxidation of N,N-dimethylaniline may be a significant loss mechanism for this chemical (Dragun and Helling, 1985). Based on its physical properties, it is predicted that this chemical may leach moderately into groundwater from contaminated soils.

3. EXPOSURE

3.1. WATER

Water from both Lake Ontario and Lake Erie was monitored for N,N-dimethylaniline by the Great Lakes Water Quality Board (1983). The compound was qualitatively detected in Lake Ontario water but not in Lake Erie water. Although not specifically identified, Kaczvinsky et al. (1983) indicated the possibility of the presence of N,N-dimethylaniline in shale oil process water. Nelson and Hites (1980) monitored sediment samples from the Buffalo River, NY, near a dye manufacturing plant. N,N-Dimethylaniline was not detected in sediment samples, although soil samples near the plant site contained up to 40 mg/kg of this compound. N,N-Dimethylaniline has also been detected in several industrial effluent samples in the United States and in several surface waters in the United States and Germany (U.S. EPA, 1976). Data regarding the detection of this compound in drinking water could not be located in the available literature as cited in the Appendix.

3.2. AIR

Monitoring data on the atmospheric level of this compound could not be located in the available literature as cited in the Appendix. The level of this compound under occupational conditions in coal liquefaction plants and a plant manufacturing fiber glass-reinforced plastic pipes was reported by Harris et al. (1980) and Markel and Wilcox (1981); N,N-dimethylaniline was either not detected or was below the OSHA standard.

3.3. FOODS

Pertinent monitoring data regarding the level of this compound in food could not be located in the available literature as cited in the Appendix.

3.4. SUMMARY

Although N,N-dimethylaniline has been qualitatively identified in several industrial effluents and surface waters (U.S. EPA, 1976), it apparently has never been detected in drinking water. No monitoring data on the ambient level of N,N-dimethylaniline in either food or air were available. The level of this compound in the occupational atmosphere of a coal liquefaction plant and a plant manufacturing fiber glass-reinforced plastic pipe was reported (Harris et al., 1980; Markel and Wilcox, 1981); the compound was either not detected or its level was below the OSHA standard.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix. Information from toxicity studies (Section 5.5.) (Abdo et al., 1984; Markosyan, 1969), however, indicate that N,N-dimethylaniline is absorbed after both inhalation and ingestion.

4.2. DISTRIBUTION

Pertinent data regarding the distribution and retention of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Based on several *in vitro* studies with rat and rabbit microsomal enzymes, it appears that N,N-dimethylaniline can undergo oxidation at the nitrogen atom or either of the methyl carbons (Hamill and Cooper, 1984; Gorrod et al., 1979; Gorrod and Gooderham, 1981). Oxidation of either of the methyl carbons results in N-dealkylation of N,N-dimethylaniline; whereas, oxidation of the nitrogen results in the formation of N,N-dimethylaniline-N-oxide (Bickel et al., 1971). The rate of N-oxidation depends on the concentration of N-oxidase, which can vary in different tissues (Ohmiya and Mehendale, 1983; Devereux and Fouts, 1974) and under different physiological conditions (Rane, 1974; Heinze et al., 1970; Uehleke et al., 1971; Devereux and Fouts, 1974). For example, the metabolism of N,N-dimethylaniline was 2 times greater in freshly isolated rabbit Clara cells as in freshly isolated rabbit pneumocyte II cells *in vitro* (Devereux et al., 1985). The ratio of the rate of N-oxidation to C-oxidation can be increased or decreased by various agents (Hlavica and Kehl, 1976; Olsson et al., 1984,

Beije and Arrhenius, 1978). For example, pretreatment of rabbits with CO (Hlavica and Kehl, 1974) and rats or guinea pigs with corticosteroids or 2-aminofluorene (Arrhenius, 1968) decreases the rate of N-oxidation; whereas, triethyl lead chloride exposure (Odenbro and Arrhenius, 1984), dimethylnitrosamine exposure (Olsson et al., 1983), vitamin E depletion, protein deficiency, and stress all increase the rate of N-oxidation (Arrhenius, 1968). Conditions that increase the ratio of the rate of N-oxidation to the rate of C-oxidation may potentiate the tumorigenicity of carcinogenic aromatic amines (Odenbro and Arrhenius, 1984; Arrhenius, 1968). Evaluation of the N-oxidase activity in human liver biopsies from >100 patients indicates that N-oxidase activity is greater in human liver tissue than in the hepatic tissue of laboratory animals (Ziegler and Gold, 1971), suggesting that the carcinogenic potential of N,N-dimethylaniline exposure may be greater in humans than in laboratory animals.

A group of eight anesthetized mongrel dogs were injected intravenously with 40 mg/kg of N,N-dimethylaniline, and their urine was collected for 48 hours (Kiese and Renner, 1974). Both conjugated and unconjugated metabolites were identified in the urine. The substances identified in the urine before incubation with glucuronidase or sulfatase included N,N-dimethylaniline, N-methylaniline, 4-aminophenol, 4-methylaminophenol, 4-dimethylaminophenol and 2-aminophenol as well as minute amounts of 2-methylaminophenol and 2-dimethylaminophenol. The same compounds were identified after hydrolysis of the urinary components. Although aniline itself was not identified in the urine, it has been found in the blood of dogs injected with N,N-dimethylaniline. N,N-Dimethylaniline-N-oxide was not found in the urine.

As reviewed in Kiese and Renner (1974) and Kiese et al. (1966), earlier studies reported the presence of p-dimethylaminophenol in the urine of

rabbits (Hildebrandt, 1907) and rats (Elson et al., 1946) treated with N,N-dimethylaniline. The hydroxylated metabolites may have resulted from the oxidation of the ring carbons.

4.4. EXCRETION

Quantitative data regarding the excretion of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix. Kiese and Renner (1974) reported that eight compounds (N,N-dimethylaniline, N-methylaniline, 4-aminophenol, 4-methylaminophenol, 4-dimethylaminophenol 2-aminophenol, 2-methylaminophenol and 2-dimethylaminophenol) were identified in the urine of dogs after intravenous administration of 40 mg/kg of N,N-dimethylaniline, but quantitative data on the percent of an oral or inhalation dose that is excreted in the urine, feces, bile and expired air, and on the half-life of N,N-dimethylaniline after administration, were not obtained from that study.

4.5. SUMMARY

Quantitative data regarding the absorption of N,N-dimethylaniline could not be located in the available literature, although toxicity studies (Abdo et al., 1984; Markosyan, 1969) indicate that N,N-dimethylaniline is absorbed after both inhalation and ingestion. Pertinent data regarding the distribution, retention and excretion of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix. N,N-Dimethylaniline can undergo oxidation at either of the methyl carbons or at the nitrogen (Bickel et al., 1971). The rate of N-oxidation depends on the concentration of N-oxidase (Ohmiya and Mehendale, 1983). Conditions that increase the ratio of N-oxidation to C-oxidation may potentiate the tumorigenicity of carcinogenic aromatic amines (Odenbro and Arrhenius, 1984; Arrhenius, 1968).

Metabolites of N,N-dimethylaniline found in the urine of dogs treated intravenously with 40 mg/kg of N,N-dimethylaniline included N,N-dimethylaniline, N-methylaniline, 4-aminophenol, 4-methylaminophenol, 4-dimethylaminophenol, 2-aminophenol, as well as minute amounts of 2-methylaminophenol and 2-dimethylaminophenol (Kiese and Renner, 1974). 2-Dimethylaminophenol has also been identified in the urine of rabbits (Hildebrandt, 1907) and rats (Elson et al., 1946). The appearance of the phenols indicate that N,N-dimethylaniline can also undergo oxidation at the ring carbons.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix; however, aniline (NCI, 1978) and 2,4-dimethylaniline (Weisburger et al., 1978) are both carcinogenic. Dietary aniline was associated with an increased incidence of a variety of tumors including splenic hemangiosarcoma and peritoneal fibromas. The chronic quality assessment of a bioassay in which rats and mice were treated by gavage with N,N-dimethylaniline for 2 years is currently in progress (NTP, 1986).

5.2. MUTAGENCITY

Pertinent data regarding the mutagenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix. Although Klopman et al. (1985) reported that the Connor et al. (1983) study found N,N-dimethylaniline not to be mutagenic to Salmonella typhimurium, N,N-dimethylaniline was not among the 19 chemicals evaluated by Connor et al. (1983).

5.3. TERATOGENICITY

Groups of 50 mated CD-1 albino mice were treated by gavage with 0 or 365 mg/kg/day (MTD) of N,N-dimethylaniline in corn oil on days 7-14 of gestation (Piccirillo et al., 1983). The dose was selected from a dose range-finding study in which 365 mg/kg day, the lowest dose tested, resulted in the death of 3/10 mice. The three deaths were considered to be compound-related. The endpoints evaluated in the reproductive study included maternal and pup body weights and mortality, as well as litter counts within 12 hours of birth and on postpartum day 3. No significant effect on maternal body weight or litter weight 3 days postpartum was observed in the mice treated with

N,N-dimethylaniline, although both parameters were slightly decreased when compared with control values. The average litter weight at birth was reported to be significantly higher in the treated group (1.7±0.2) than in the control group (1.5±0.1). Three dams in the N,N-dimethylaniline group died; there were no deaths in the control group. Seven dams in the N,N-dimethylaniline group were not pregnant, nine in the control group. Three dams in the treated group, but none in the control group, had been fertilized without subsequent implantation (determined by presence of corpora lutea upon examination of uteri at necropsy). One dam in the treated group had a dead litter which was not delivered by day 23 of gestation. The average number of live pups per litter at birth was 9±3 for the control group and 9±3 for the treated group. The average number of live pups per litter 3 days postpartum was 9±3 for the control group and 8±3 for the treated group. Although the Offspring Viability Ratio (number of live pups on day 3 postpartum/number of live pups at birth) was reported to be significantly (Student's t-test) reduced in the treated group compared with the control group, the reported mean ratios [0.98±0.04 (SD) for treated vs. 1.00±0.02 (SD) for controls] do not appear to be different. Moreover, the investigators stated that there were no adverse effects on viability through the first 3 postpartum days.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only toxicity studies available were the subchronic (13-week) toxicity tests of N,N-dimethylaniline in rats and mice (Springborn Institute

for Bioresearch, Inc., 1980; Abdo et al., 1984) and the abstract of a 100-day Russian inhalation study in rats (Markosyan, 1969).

Abdo et al. (1984) described a subchronic oral toxicity study of the effects of N,N-dimethylaniline in F344 rats and B6C3F1 mice. Groups of 10 male and 10 female F344 rats and 10 male and 10 female B6C3F1 mice were treated by gavage with 0, 31.25, 62.5, 125.0, 250 or 500 mg/kg/day of N,N-dimethylaniline in corn oil, 5 days/week for 13 weeks. The final report of this subchronic study (Springborn Institute for Bioresearch, Inc., 1980) includes additional experimental data which are summarized in Table 5-1. The endpoints evaluated included body weight, mortality, clinical signs of intoxication (cyanosis, blanching, changes in motor activity), spleen size and splenic, hepatic, renal and testicular histology. No effect was observed on the mortality rate in the rats. There was a significantly decreased body weight gain in the male rats, but not the females, treated with 250 or 500 mg/kg/day. Salivation after dosing occurred at all dose levels in both male and female rats, but not after treatment with corn oil in control rats. Excessive urination occurred in 1/10 female rats treated with 31.25 mg/kg/day of N,N-dimethylaniline, 2/10 female rats treated with 62.5 mg/kg/day and in all the females treated with $\geq$125 mg/kg/day. Changes in motor activity occurred in both male and female rats treated with $\geq$125 mg/kg/day. Cyanosis and blanching were also observed in males and females at the three highest dose levels tested. Bone marrow hyperplasia was reported in males and females treated with 500 mg/kg/day of N,N-dimethylaniline. Increased hemosiderosis was observed in the livers of male and female rats treated with 125 mg/kg/day, in the kidneys of female rats treated with 250 mg/kg/day and in the kidneys and testes of male rats treated with 500 mg/kg/day. Hemosiderosis and hematopoiesis were observed

TABLE 5-1

Summary Toxicity Table for the Subchronic Gavage Study of N,N-Dimethylaniline in F344 Rats and B6C3F1 Mice*

Species	Sex	Dose (mg/kg)	Mortality	Weight Gain (g)	Clinical Signs	Gross Observations	Pathology
Rat	M	0 (control)	0/10	223	Not remarkable	No significant gross lesions	No significant microscopic alterations
Rat	M	31.25	0/10	208	Salivation after dosing	Minimal splenomegaly, 10/10 rats	Spleen: chronic congestion, mild hemosiderosis, hematopoiesis
Rat	M	62.5	0/10	204	Salivation after dosing, motor activity decrease (1)	Mild splenomegaly, 10/10 rats	Spleen: chronic congestion, mild hematopoiesis, moderate hemosiderosis
Rat	M	125	0/10	195	Salivation after dosing, motor activity decrease, blanching	Moderate splenomegaly, 10/10 rats	Spleen: chronic congestion, moderate to severe hematopoiesis, moderate hemosiderosis
Rat	M	250	0/10	169	Salivation after dosing, decrease and cyanosis, motor activity increase, blanching	Severe splenomegaly, 10/10 rats	Spleen: chronic congestion, severe hemosiderosis and hematopoiesis
Rat	M	500	1/10	129	Salivation after dosing, motor activity decrease, motor activity increase, cyanosis, blanching, mortality	Severe splenomegaly, dark reddish-brown kidneys, 10/10 rats	Spleen: severe hematopoiesis and hemosiderosis Kidneys: severe hemosiderosis; cholemic nephrosis Liver: diffuse hemosiderosis of Kupffer cells Testes: focal minimal hemosiderosis Bone marrow: hyperplasia of hematopoietic cells
Rat	F	0 (control)	0/10	90	Not remarkable	No significant gross lesions	No significant microscopic alterations
Rat	F	31.25	0/10	92	Salivation after dosing, excessive urination (1)	Minimal splenomegaly, 10/10 rats	Spleen: chronic congestion; mild hemosiderosis and hematopoiesis
Rat	F	62.5	1/10	92	Salivation after dosing, excessive urination (2), killed - prolapsed eye (1)	Mild splenomegaly, 10/10 rats	Spleen: chronic congestion; mild hematopoiesis; moderate hemosiderosis
Rat	F	125	1/10	88	Salivation after dosing, motor activity decrease, excessive urination, blanching, mortality	Severe splenomegaly, 10/10 rats	Spleen: chronic congestion; severe hematopoiesis, moderate hemosiderosis

TABLE 5-1 (cont.)

Species	Sex	Dose (mg/kg)	Mortality	Weight Gain (g)	Clinical Signs	Gross Observations	Pathology
Rat	F	250	1/10	85	Salivation after dosing, motor activity decrease, motor activity increase, cyanosisi, blanching, excessive urination	Severe splenomegaly, 10/10 rats	Spleen: chronic congestion; severe hematopoiesis and hemosiderosis
Rat	F	500	0/10	84	Salivation after dosing, motor activity decrease, motor activity increase, cyanosis, blanching, excessive urination	Severe splenomegaly, dark reddish-brown kidneys, 10/10 rats	Spleen: severe hematopoiesis and hemosiderosis Liver: diffuse hemosiderosis of Kupffer cells Bone marrow: hyperplasia of hematopoietic cells
Mouse	M	0 (control)	1/10	8	Motor activity decrease, rought coat, morbidity, mortality	No significant gross lesions	No significant mic oscopic alterations
Mouse	M	31.25	2/10	6	Salivation after dosing, motor activity decrease, morbidity, mortality	Minimal splenomegaly, 4/10 mice	Spleen: mild increase in hematopoiesis 1/10 mice, remaining spleens appeared to be within normal histological limits
Mouse	M	62.5	3/10	5	Salivation after dosing, motor activity decrease, rough coat, morbidity, mortality	Minimal splenomegaly, 7/10 mice	Spleen: minimal to mild hematopoiesis and hemosiderosis 7/10 mice
Mouse	M	125	0/10	5	Salivation after dosing, motor activity decrease, blanching	Minimal splenomegaly, 10/10 mice	Spleen: minimal to mild hematopoiesis and hemosiderosis 7/10 mice
Mouse	M	250	1/10	8	Salivation after dosing, motor activity decrease, blanching, mortality	Minimal to mild splenomegaly, 10/10 mice	Spleen: mild to moderate hematopoiesis, 10/10 mice
Mouse	M	500	0/10	5	Salivation after dosing motor activity decrease, blanching	Moderate splenomegaly, 10/10 mice	Spleen: severe hematopoiesis and hemosiderosis Liver: diffuse hemosiderosis of Kupffer cells Kidney: mild hemosiderosis
Mouse	F	0 (control)	0/10	5	Not remarkable	No significant gross lesions	No significant microscopic alterations

TABLE 5-1 (cont.)

Species	Sex	Dose (mg/kg)	Mortality	Weight Gain (g)	Clinical Signs	Gross Observations	Pathology
Mouse	F	31.25	0/10	2	Salivation after dosing	Minimal splenomegaly, 4/10 mice	Spleen: appeared to be within normal histological limits
Mouse	F	62.5	1/10	4	Salivatin after dosing, mortality	Minimal splenomegaly, 8/10 mice	Spleen: minimal to mild hematopoiesis and hemosiderosis 8/10 mice
Mouse	F	125	0/10	3	Salivation after dosing, motor activity decrease, blanching	Minimal splenomegaly, 10/10 mice	Spleen: minimal to mild hematopoieis and hemosiderosis, 10/10 mice
Mouse	F	250	0/10	4	Salivation after dosing, motor activity decrease, blanching	Minimal to mild splenomegaly, 10/10 mice	Spleen: mild to moderate hematopoiesis and hemosiderosisi, 10/10 mice
Mouse	F	500	0/10	5	Salivation after dosing, motor activity decrease, blanching	Moderate splenomegaly, 10/10 mice	Spleen: severe hem topoiesis and hemosiderosis Liver: diffuse hemosiderosis of Kupffer cells, minimal hematopoiesis Kidney: minimal hemosiderosis

*Source: Springborn Institute for Bioresearch, Inc., 1980

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in the spleens of treated male and female rats at all dose levels and increased in severity as the dose levels of N,N-dimethylaniline increased. Splenomegaly was observed in male and female rats at all dose levels tested, although reported to be minimal and mild at the 31.25 and 62.5 mg/kg/day dose levels, respectively. Splenomegaly, hematopoiesis and hemosiderosis were not observed in the control rats. In mice, no dose-related effect was observed on the mortality rate in either males or females. Although no significant effect on body weight was observed in the mice, the average body weight of males treated with N,N-dimethylaniline was less than the body weight of control males at all dose levels tested. Salivation after dosing occurred in male and female mice at all dose levels tested, but not in controls. Change in motor activity occurred at all dose levels in the male mice, but only at $\geq$125 mg/kg/day in the female mice. Blanching, but not cyanosis, was reported in male and female mice treated with $\geq$125 mg/kg/day. Increased hemosiderosis was observed in the livers of male and female mice only at 500 mg/kg/day. Minimal splenomegaly without hemosiderosis or hematopoiesis was observed in <50% of the male and female mice treated with 31.25 mg/kg/day. Splenomegaly accompanied by hemosiderosis and minimal to mild hematopoiesis was reported in ~75% of the male and female mice treated with 62.5 mg/kg/day and occurred in all male and female mice treated with $\geq$125 mg/kg/day.

The abstract of a Russian study (Markosyan, 1969) reported changes in muscle chronaxy, increased methemoglobin levels, and decreased hemoglobin and number of erythrocytes, reticulocytosis, leukopenia and increased levels of urinary coproporphyrin in rats inhaling 0.3 mg/m^3 N,N-dimethylaniline continuously for 100 days. No adverse effects were observed in the rats exposed to 0.04 or 0.005 mg/m^3 of N,N-dimethylaniline continuously for 100 days. No additional details were reported.

5.6. OTHER RELEVANT INFORMATION

NIOSH (1986) reported the oral LD_{50} in rats to be 1410 mg/kg and the oral LD_{Lo} in humans to be 50 mg/kg. The ACGIH (1986) reported that a single oral dose of 50 mg/kg produced methemoglobinemia in dogs.

N,N-Dimethylaniline may be a contaminant in some commercial preparations of penicillins and cephalosporins (Margosis, 1977; Quercia et al., 1980).

The odor of dimethylaniline (isomer unspecified) can be detected at 0.013 ppm (Amoore and Hautala, 1983), which is well below the air level of 5 ppm permitted by the ACGIH (1986) in the workplace.

5.7. SUMMARY

Pertinent data regarding the carcinogenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix, but a chronic gavage study in rats and mice is in progress (NTP, 1986). The mutagenicity of N,N-dimethylaniline has not been evaluated. No effects on survival or weight gain of dams or birth weight, weight gain and viability of offspring were observed in mice treated by gavage with 365 mg/kg/day of N,N-dimethylaniline in corn oil on days 7-14 of gestation (Piccirillo et al., 1983). The chemical has not been studied adequately for teratogenicity. The final report on the subchronic phase of the NCI bioassay on N,N-dimethylaniline (Abdo et al., 1984; Springborn Institute for Bioresearch, Inc., 1980) indicated that splenomegaly and splenic hemosiderosis and hematopoiesis were observed in male and female rats treated by gavage (corn oil vehicle) with a dose of N,N-dimethylaniline $\geq$31.25 mg/kg/day (lowest dose tested) for 13 weeks. At dose levels $\geq$125 mg/kg/day, hepatic hemosiderosis was observed. At higher dose levels, renal and testicular hemosiderosis was reported. Splenomegaly without splenic hemosiderosis was reported in half of the mice treated with 31.25 mg/kg/day (lowest dose

tested) for 13 weeks. At the next highest dose tested (62.5 mg/kg/day), splenomegaly and splenic hemosiderosis occurred in 75% of the mice. Changes in the murine liver and kidney were reported only at the highest dose tested (500 mg/kg/day). The abstract of a Russian study (Markosyan, 1969) indicated that hematopoietic effects were observed in rats after continuous inhalation exposure to N,N-dimethylaniline for 100 days at 0.3 mg/m^3 but not at 0.04 mg/m^3.

6. AQUATIC TOXICITY

6.1. ACUTE

The only information available was provided by Tonogai et al. (1982), who reported 24- and 48-hour LC_{50} values of 56 and 33 mg/ℓ N,N-dimethylaniline for the medaka, Oryzias latipes, and by Broderius and Kahl (1985) who reported a 96-hour LC_{50} value of 65.6 mg/ℓ for fathead minnows, Pimephales promelas.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

In an algal lawn bioassay, concentrations of 0.1-1000 µg/dish had no effect on growth of the marine blue-green alga, Agmenellum quadruplicatum (Batterton et al., 1978). Armstrong et al. (1981) reported that 5 mg/ℓ increased the activity of phosphodiesterase in the alga, Cyclottella meneghiniana, but had no effect an alkaline phosphatase activity.

6.4. RESIDUES

Pertinent data regarding residues of N,N-dimethylaniline in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

The only toxicologically significant information concerning effects of N,N-dimethylaniline on aquatic organisms was provided by Tonogai et al. (1982), who reported 24- and 48-hour LC_{50} values of 56 and 33 mg/ℓ, respectively, for the medaka, Oryzias latipes, and by Broderius and Kahl (1985) who reported a 96-hour LC_{50} of 65.6 mg/ℓ for fathead minnows, Pimephales promelas.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1985, 1986) adopted a TWA-TLV of 5 ppm (25 mg/m³) with a STEL of 10 ppm (50 mg/m³) for N,N-dimethylaniline based on its similar toxicity to aniline, including methemoglobin formation and its depressant effect on the nervous system. The skin notation is used by the ACGIH (1985, 1986) to indicate that the potential contribution from percutaneous absorption is substantial. OSHA (1985) also recommends an occupational exposure limit of 5 ppm (~25 mg/m³) and cautions that percutaneous absorption may contribute a substantial amount of N,N-dimethylaniline to the body burden of an exposed individual.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix, but a chronic gavage study in rats and mice is in progress (NTP, 1986). The mutagenicity of N,N-dimethylaniline has not been evaluated. No effects on survival or weight gain of dams or birth weight, weight gain or viability of offspring were observed in mice treated by gavage with 365 mg/kg/day of N,N-dimethylaniline in corn oil on days 7-14 of gestation (Piccirillo et al., 1983). The chemical has not been studied adequately for teratogenicity. The final report on the subchronic phase of the NCI bioassay on N,N-dimethylaniline (Abdo et al., 1984; Springborn Institute for Bioresearch, Inc., 1980) indicated that splenomegaly and splenic hemosiderosis and hematopoiesis were observed in male and female rats treated by gavage (corn oil vehicle) with a dose of N,N-dimethylaniline $\geq$31.25 mg/kg/day (lowest dose tested) for 13 weeks. At dose levels $\geq$125 mg/kg/day, hepatic hemosiderosis was observed. At higher dose levels, renal and testicular hemosiderosis was reported. Splenomegaly without splenic hemosiderosis was reported in half of the mice treated with 31.25 mg/kg/day (lowest dose tested) for 13 weeks. At the next highest dose tested (62.5 mg/kg/day), splenomegaly and splenic hemosiderosis occurred in 75% of the mice. Changes in the murine liver and kidney were reported only at the highest dose tested (500 mg/kg/day). The abstract of a Russian study (Markosyan, 1969) indicated that hematopoietic effects were observed in rats after continuous inhalation exposure to N,N-dimethylaniline for 100 days at 0.3 mg/m^3 but not at 0.04 mg/m^3.

Although the subchronic gavage study in rats and mice did not establish a NOEL or NOAEL for oral exposure, an RfD (formerly called ADI) of 0.002 mg/kg/day or 0.2 mg/day for a 70 kg man can be derived by multiplying the LOAEL of 31.25 mg/kg/day by 5/7 days and dividing by an uncertainty factor of 10,000 (10 for interspecies extrapolation, 10 to protect sensitive individuals, 10 because the effect level was a LOAEL and 10 to approximate chronic exposure).

The Russian study by Markosyan (1969) reported hematological effects in rats exposed continuously by inhalation to 0.3 mg/m^3 for 100 days, while no effects were reported at 0.04 mg/m^3. Multiplying these exposures by 0.223 m^3/day (the breathing volume of a rat), by an absorption factor of 0.5 and dividing by the reference rat weight of 0.35 kg, results in equivalent oral doses of 0.1 and 0.01 mg/kg/day, respectively. Although these doses appear to represent a lower LOAEL and a NOEL, respectively, the study is inappropriate for RfD derivation because it was reported in limited detail, histological examination was not performed and uncertainties are inherent in the route-to-route extrapolation. Furthermore, because of these limitations, the study cannot be considered supportive of the oral RfD.

Since the subchronic oral study failed to establish a NOAEL or NOEL and since the inhalation study provides inadequate support, low confidence is placed on the study of choice for the RfD, the data base and the RfD. Therefore, the RfD of 0.002 mg/kg/day should be considered provisional. Results of a chronic oral bioassay in rats and mice (NTP, 1986), which will address carcinogenicity, chronic toxicity and mutagenicity, are not yet available.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The primary effect of either oral (Springborn Institute for Bioresearch, Inc., 1980) or inhalation (Markosyan, 1969) exposure to N,N-dimethylaniline appears to occur in the hematopoietic system, which is due to increased methemoglobinemia (Table 9-1).

Splenomegaly accompanied by splenic hemosiderosis and hematopoiesis was judged to be the earliest indicator of this syndrome in the subchronic study (Springborn Institute for Bioresearch, Inc., 1980); therefore, the increased hemosiderosis seen at higher dose levels in the liver, kidney and testis were not scored as separate effects of N,N-dimethylaniline exposure, but were considered to be magnifications of the adverse effects observed in the spleens at the lowest dose tested. Both male and female rats had splenomegaly accompanied by mild hemosiderosis and hematopoiesis when treated by gavage with 31.25 mg/kg/day, 5 days/week for 13 weeks. The average body weight for the male and female rats was experimentally determined to be 0.17 and 0.27 kg, respectively. Therefore, the chronic human MED, obtained by multiplying the animal dose of 31.25 mg/kg/day by 5/7 days and by the cube root of the ratio of the female rat body weight to the reference human body weight $(0.17/70)^{1/3}$ and by 70 kg, and dividing by 10 to account for the use of a subchronic study to derive a chronic human MED, is 21.0 mg/day. The RV_d associated with the MED of 21.0 mg/day is 3.5. Splenomegaly accompanied by mildly increased splenic hemosiderosis and hematopoiesis warrants an RV_e of 7. The CS obtained by multiplying the RV_d by the RV_e is 24.5. The RQ associated with the CS is 100, as indicated in Table 9-2.

TABLE 9-1

Toxicity Summary for N,N-Dimethylaniline

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Dose/Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral	rat/F344	M/F	10/10	0.27/0.17[a]	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Splenomegaly accompanied by increased splenic hemosiderosis in males and females	Springborn Institute for Bioresearch Inc., 1980
Oral	rat/F344	M/F	10/10	0.27/0.17[a]	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Increased salivation after dosing	Springborn Institute for Bioresearch Inc., 1980
Oral	rat/F344	F	10	0.17[a]	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Excess urination	Springborn Institute for Bioresearch Inc., 1980
Oral	rat/F344	M	10	0.27[a]	corn oil	>99.9%	62.5 mg/kg/day 5 days/week	44.64	Change in motor activity	Springborn Institute for Bioresearch Inc., 1980
Oral	mouse/ B6C3F1/ GLBR	M/F	10/10	0.032 (M)/[a] 0.025 (F)	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Splenomegaly without histological alteration; hemosiderosis and hematopoiesis occurred at higher dose levels	Springborn Institute for Bioresearch Inc., 1980
Oral	mouse/ B6C3F1/ GLBR	M/F	10/10	0.032 (M)/[a] 0.025 (F)	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Increased salivation after dosing	Springborn Institute for Bioresearch Inc., 1980
Oral	mouse/ B6C3F1/ GLBR	M	10	0.032[a]	corn oil	>99.9%	31.25 mg/kg/day 5 days/week	22.32	Decreased motor activity	Springborn Institute for Bioresearch Inc., 1980
Inhalation	rat	NR	NR	0.35[b]	NR	NR	0.3 mg/m³ continuously for 100 days	0.19[c]	Increased methomoglobin levels, decreased hemoglobin levels, decreased erythrocyte counts, reticulocytosis, leukopenia	Markosyan, 1969

[a]Reported by investigator

[b]Reference rat weight

[c]Calculated by multiplying exposure by 0.2332 m³/day (reference rat weight) and dividing by 0.35 kg

NR = Not reported

TABLE 9-2

Oral Composite Scores for N,N-Dimethylaniline[a]

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
Rat (F)	22.32	21.0[b]	3.5	Splenomegaly with increased splenic hemosiderosis and hematopoiesis	7	24.5	100
Mouse (F)	22.32	11.09 (F)[b]	3.9	Splenomegaly without histological alteration, increased hemosiderosis was seen at higher doses	6	23.4	100

[a]Source: Springborn Institute for Bioresearch, Inc., 1980

[b]The exposure was divided by an uncertainty factor of 10 to approximate chronic exposure.

The three other effects (see Table 9-1) observed in rats treated by gavage with 31.25 mg/kg/day, 5 days/week for 13 weeks were increased salivation after dosing, excess urination and decreased motor activity (see Table 9-1). The increased salivation appears to have been a transitory effect that occurred following dosing. It did not increase with increasing dose or increased duration of exposure. The incidence of increased urination observed in female rats was dose-related, but the biological significance of increased urination in the absence of histological alterations other than increased hemosiderosis, even at the highest dose level tested, is difficult to interpret. The methodology used to measure the decreased motor activity in rats, as well as the significance of the decreased motor activity, were not discussed in the Springborn Institute for Bioresearch, Inc. (1980) report. At some dose levels motor activity is reported to both decrease and increase. Therefore, since these parameters need further clarification to be useful for defining chronic toxicity, CSs based on increased salivation after dosing (rats and mice), increased urination (rats) and altered motor activity (rats and mice) were not derived.

The inhalation study by Markosyan (1969) (see Table 9-1) is considered to be inappropriate for RQ derivation because of the lack of experimental detail.

The primary effect of oral exposure to N,N-dimethylaniline in mice also occurs in the hematopoietic system, which is due to methemoglobin formation (Springborn Institute for Bioresearch, Inc., 1980). Both male and female mice treated by gavage with 31.25 mg/kg/day, 5 days/week for 13 weeks had enlarged spleens unaccompanied by histological changes. The average body weight for male and female mice was experimentally determined to be 0.032 and 0.025 kg, respectively. Therefore, the chronic human MED, obtained by

multiplying the animal dose of 31.25 mg/kg/day by 5/7 and by the cube root of the ratio of the female mouse body weight to the human body weight $(0.025/70)^{1/3}$, and by 70 kg, and dividing by 10 to account for the use of a subchronic study to derive a chronic human MED, is 11.1 mg/day. The RV_d associated with an MED of 11.1 mg/day is 3.9. The RV_e associated with splenomegaly accompanied by histological changes was determined to be 6. The CS, obtained by multiplying the RV_d by the RV_e, is 23.4. The RQ associated with a CS of 23.4 is 100.

As indicated in Table 9-2 and reported in Table 9-3, the most appropriate RQ for N,N-dimethylaniline from the available data is 100, based on the CS of 24.5 obtained from the hematopoietic effects reported in female rats by the Springborn Institute for Bioresearch, Inc. (1980). An RQ of 100 is supported by the hematopoietic effects reported in male rats and in male and female mice (Springborn Institute for Bioresearch, Inc., 1980).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Because data regarding the carcinogenicity of N,N-dimethylaniline could not be located in the available literature as cited in the Appendix, a potency factor cannot be derived.

IARC has not evaluated the carcinogenicity of N,N-dimethylaniline (NIOSH, 1986). According to U.S. EPA (1984), N,N-dimethylaniline belongs in CAG Group D; that is, animal and human evidence currently available is inadequate to evaluate the carcinogenicity of N,N-dimethylaniline. These classifications may change pending the results of the NTP (1986) study.

TABLE 9-3

N,N-Dimethylaniline

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	21.0 mg/day
Effect:	splenomegaly accompanied by increased splenic hemosiderosis and hematopoiesis in female rats
Reference:	Springborn Institute for Bioresearch, Inc., 1980
RV_d:	3.5
RV_e:	7
Composite Score:	24.5
RQ:	100

*Equivalent human dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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